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NDA: 21-153

Approvable Letter for NDA 21-153

October 3, 2000

Excerpted pages from: http://www.fda.gov/cder/foi/nda/2001/21154_Nexium_Approv[1].pdf

Downloaded: October 4, 2005

NDA 21-153 OCT 3 2000

AstraZeneca LP
Attention: Gary P. Horowitz, Ph.D.
725 Chesterbrook Blvd.
Mailcode: E-3C
Wayne, PA 19087-5677

Dear Dr. Horowitz:

Please refer to your new drug application (NDA) dated December 3, 1999, received December 3, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nexium (esomeprazole magnesium) Delayed-Release Capsules.

We acknowledge receipt of your submissions dated December 13 and December 22, 1999; and January 19, January 31, March 3, March 17, April 3. April 27. June 1, June 5, June 23, July 17, August 2, August 4, August 14, August 16, and August 25, 2000.

This new drug application provides for the following proposed indications: 1) healing of erosive esophagitis; 2) maintenance of healing of erosive esophagitis: and 3) treatment of symptomatic gastroesophageal reflux disease.

We note that NDA 21-154 for Nexium (esomeprazole magnesium) Delayed-Release Capsules was submitted to the Division of Special Pathogen and Immunologic Drug Products on February 28, 2000 for the following proposed indication: eradication of *Helicobacter pylori* in patients with duodenal ulcer disease or a history of duodenal ulcer disease.

We have completed the review of NDA 21-153, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

1. Regarding the drug substance impurities:

   Provide descriptions of the methods for determination of the following materials, including validation data (Page 004-002-056):

   [ ]

   Please be advised that the acceptability of not including tests for these possible impurities in the release specifications (e.g. not testing for ——— depends on complete information about the testing performed as part of the characterization of the drug

substance esomeprazole magnesium.

2. Provide data to demonstrate that the blister packaging used for the unit dose packages of 100 are child resistant.

In addition, it will be necessary for you to submit revised draft labeling for the drug. The labeling should be identical in content to the enclosed marked-up labeling (text for the package insert). Please note that the proposed indication for the eradication of *Helicobacter pylori* is not addressed in the enclosed labeling (affected text appears in gray). This indication and all sections of the labeling that pertain to this indication are currently under review by the Division of Special Pathogen and Immunologic Drug Products and will be addressed under NDA 21-154.

We also have the following recommendations regarding the container labels and the unit dose blister package:

1. The following statement should be placed on all container labels if space permits:

   "Each delayed-release capsule, for oral administration, contains esomeprazole magnesium trihydrate equivalent to 20 mg or 40 mg esomeprazole. In addition, each capsule contains the following inactive ingredients..."

2. The "net quantity" on all container labels should be relocated and not appear in conjunction with the established name so it is not confused for the product strength.

3. The established name should be revised on the unit dose blister package to read "Delayed-Release Capsule" rather than "Delayed-Release Capsules."

We note that you have not provided labels for the ——— count physician samples.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Maria R. Walsh, M.S., Project Manager, at (301) 443-8017.

APPEARS THIS WAY
ON ORIGINAL

Sincerely,

/S/ 10/3/00

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 21-153
HFD-180/Div. Files
HFD-180/M.Walsh
HFD-180/H.Gallo-Torres
A.Shaw
L.Zhou
J.Choudary
HFD-870/S.Al-Fayuomi
S.Doddapaneni
HFD-715/Y.Tsong
T.Permutt
HFD-002/ORM
HFD-103/ADRA
HFD-42/DDMAC (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

APPEARS THIS WAY
ON ORIGINAL

Drafted by: M.Walsh 9/25/00
Initialed by: A.Shaw 9/28/00, 10/3/00
L.Zhou 9/25/00, 9/28/00
J.Choudary 9/27/00
S.Aurecchia 10/2/00, 10/3/00
Revised: M.Walsh 10/2/00, 10/3/00
final: M.Walsh 10/3/00
filename: _____

APPROVABLE (AE)

There are no phase 4 committments.

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NDA: 21-154

Pharmacology/Toxicology Review and Evaluation

October 31, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-153/ 21-154

STATISTICAL REVIEW(S)

PHARMACOLOGY / TOXICOLOGY REVIEW AND EVALUATION

NDA#: 21-154
Serial Number: 000
Type: Original Application
Date of Submission: 2/28/00

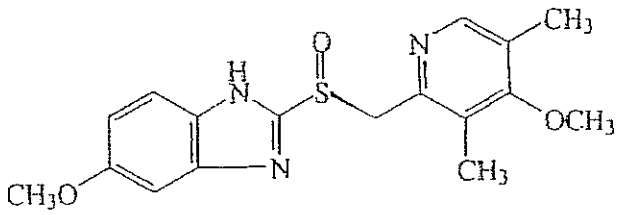
Review Division: Special Pathogen and Immunologic Drug Products
HFD-590
Reviewer: Stephen G. Hundley, Ph.D., Pharmacologist
Review Completion Date: 10/31/00

Sponsor: AstraZeneca LP
725 Chesterbrook Blvd.
Wayne, PA 19807-5677
Phone: 610-695-1008

Drug Information
Name: Esomeprazole (S-Omeprazole or H 199/18)
Drug Name: Nexium™ (Esomeprazole magnesium)
Chemical Name: Bis (5-methoxy-2-[(S)-[(4-methoxy-3.5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1*H*-benzimidazole-1-yl) magnesium salt

Free base: 5-Methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1*H*-benzimidazole-1-yl

CAS#'s: 217087-09-7 (Magnesium trihydrate)
73590-58-6 (Free base)
Molecular Formula: $(C_{17}H_{18}N_3O_3S)_2$ Mg • $3H_2O$ (Magnesium trihydrate)
$C_{17}H_{19}N_3O_3S$ (Free base)
Molecular Weight: 767 (Magnesium trihydrate), 345.4 (Free base)
Molecular Structure: Free Base



S-Omeprazole (Esomeprazole)

Drug Category: Parietal cell proton pump inhibitor

Related Submissions: IND's: ——————————
NDA's: 20-916; 19-810; and 21-153

Proposed Indication: Eradication of *Helicobacter pylori* in the treatment of —— ulcers ——— in combination therapy with amoxicillin (1g, bid) and clarithromycin (500 mg, bid).

BACKGROUND

Omeprazole, marketed as Prilosec®, is approved for use as therapy for gastroesophageal reflux disease and erosive esophagitis. Secretion of gastric acid from parietal cells is blocked due to the inhibition by omeprazole of the H+/K+ ATPase enzyme (proton pump). Omeprazole is a racemic mixture of the R- and S-enantiomers with both enantiomers exhibiting proton-pump inhibition activity. Omeprazole in combination with the antibiotics clarithromycin (500 mg, bid) and amoxicillin (1 g, bid) was evaluated and approved as a 14-day dosing regimen for *Helicobacter pylori* eradication. Numerous literature citations indicated combined acid supression/antimicrobial therapy was more effective against *H. pylori* than antimicrobial therapy alone. Increased gastric pH evidently enhanced the effect of antimicrobials against *H. pylori*.

In the current submission the sponsor evaluated the clinical efficacy of the S-enantiomer of omeprazole as the magnesium salt (esomeprazole magnesium) in combination therapy with clarithromycin and amoxicillin for eradication of *H. pylori*. The evaluated dosing regimen was 40 mg of esomeprazole magnesium (Nexium™) with clarithromycin (500 mg, bid) and amoxicillin (1 g, bid) for a period of ten days.

The sponsor previously submitted to the Division of Gastrointestinal and Coagulation Drug Products (HFD-180) an NDA package (NDA 21-153; 12/3/99 submission date) on esomeprazole magnesium for the treatment of gastroesophageal reflux disease and erosive esophagitis. The nonclinical pharmacology/toxicology reports contained in NDA 21-153 were evaluated and the Pharmacologist's Review was completed on 8/8/00. The current Pharmacology/Toxicology Review relies upon evaluations and conclusions of the Pharmacology Reviewer from HFD-180. The nonclinical pharmacology/toxicology studies submitted to NDA 21-153 are listed in the following section.

NONCLINICAL STUDIES

Expert Report on Omeprazole Toxicological and Pharmacological Documentation.

Addendum to Expert Report on Omeprazole Toxicological and Pharmacological Documentation.

Gastric Acid Secretion after a Single Dose of Omeprazole Sodium, H 199/18 Sodium, or H 199/19 Sodium in Female Rats (Report Number 3222-0353).

Effect of Omeprazole and Its Enantiomers on Acid Formation in Isolated Glands (Report Number 222-0123-00).

Pharmacokinetic Study of Omeprazole Sodium, H 199/18 Sodium, and H 199/19 Sodium Following Single Intravenous and Intraduodenal Administration in the Rat (Report Number 3222-0336).

Pharmacokinetic Study of Omeprazole and H 199/18 Magnesium Following Repeated Oral Administration in the Dog (Report Number 23870).

Excretion and Metabolism of H 199/18-^{14}C in Dogs after Oral Administration – A Comparison with [^{14}C] Omeprazole (Report Number 23992).

Study of any *In Vivo* Racemization of H 199/18 and H 199/19 in the Rat (Report Number 3222-0320).

Comparison of the Single Dose Toxicity of H 199/18 Sodium, H 199/19 Sodium, and Omeprazole Sodium in Rats after Oral Administration (Report Number T2816).

Comparison of the General Toxicity of H 199/18 Sodium, H 199/19 Sodium, Omeprazole Sodium, and Omeprazole Given Orally to Rats for 1 Month (Report Number T2823).

Toxicokinetics and Thyroid Hormone Levels after 1 Month's Oral Administration of H 199/18 Sodium, H 199/19 Sodium, Omeprazole Sodium, and Omeprazole in Rats (Report Number T2822).

H 199/18 Magnesium: Three-month Oral General Toxicity Study in Wistar Rats – A Comparison with Omeprazole (Report Number SR97477-01).

H 199/18 Magnesium: 3 Month Oral (Gavage) Toxicity in the Dog – A Comparison with Omeprazole Magnesium (Report Number SR97103 – 01).

H 199/18 Magnesium: Oral Dose Finding Embyro-Fetal Development Study in the Rat, A Comparison Study with Omeprazole (Report Number SR97207-01).

H 199/18 Magnesium: Oral Embryo-Fetal Development Study in the Rat, a Comparison with Omeprazole (Report Number 97469-01).

H 199/18 Magnesium: Oral Dose Finding Embryo-Fetal Development in the Rabbit, A Comparison Study with Omeprazole (SR97325-01)

H 199/18 Magnesium: Effects in pregnant Rabbits and a Toxicokinetic Evaluation When Given Orally (Report Number SR98107).

H 199/18 Magnesium: Effects on Pregnant Rabbits and a Toxicokinetic Evaluation after Oral Administration (Report Number SR98344-02).

H199/18 Magnesium: Oral Embryo-Fetal Development Study in the Rabbit. A comparison with Omeprazole (Report Number SR98498-01).

Mutagenicity Evaluation of H 199/18 Sodium in the Ames Salmonella/Mammalian Microsome Mutagenicity Test (Report Number T2817).

H 199/18 Magnesium: In Vitro Cytogenetic Test Using Human Peripheral Blood Lymphocytes (Report Number SR98045-01).

H 199/18 Magnesium and Omeprazole: Comparison of Solubilities (Report Number SR98232-01).

Mouse Micronucleus Test of H 199/18 Magnesium Given by Gavage (Report Number SR97484-01).

H 199/18 Magnesium: Induction of Chromosome Aberrations in the Bone Marrow of Treated Rats (Report Number SR98457-01).

Omeprazole Magnesium: Pharmacological-Toxicological Expert Report (Report Number 97164-7).

EVALUATION AND CONCLUSIONS

The sponsor submitted several repeat-dose toxicity studies comparing H 199/18 (S-omeprazole), H 199/19 (R-omeprazole), and omeprazole (racemate). The Pharmacology/Toxicology Review from HFD-180 indicated that each test compound produced equivalent toxicological effects in each of two strains of rats and in beagle dogs. The toxicity from esomprazole magnesium (the magnesium trihydrate of S-omeprazole) was shown to be equivalent to omeprazole in 3-month oral dosing studies in Wistar rats and beagle dogs. Esomeprazole magnesium (H 199/18 magnesium) was also evaluated in embryo-fetal development studies (Segment II reproductive toxicity) in rats and rabbits. Results from these studies were in agreement with prior results obtained with omeprazole. Finally, the results from a battery of genetic toxicology studies with esomprazole magnesium were in agreement with results obtained in prior submissions with omeprazole.

The comprehensive review conducted by the Pharmacology/Toxicology Reviewer in HFD-180 indicated that esomeprazole magnesium was toxicologically equivalent to omeprazole. Consequently, the Reviewer had no safety concerns with an oral dosing

regimen of 40 mg Nexium™ administered daily for a period of time up to eight weeks for treatment of gastroesophageal reflux disease or erosive esophagitis. The proposed dosing regimen for eradication of *Helicobacter pylori* in the current NDA includes 40 mg of Nexium™ daily for a period of 10 days. There are no nonclinical safety concerns with regard to this Nexium™ dosing regimen. The proposed daily dosing regimens for clarithromycin (500 mg, bid) and amoxicillin (1 g, bid) for a period of ten days are consistent with currently approved dosing regimens for these two drug products. The proposed triple therapy dosing regimen is also consistent with the currently approved triple therapy dosing regiment for Prilosec® (omeprazole).

KEYWORDS: Esomeprazole, Proton Pump Inhibitor, *Helicobacter pylori*, Nonclinical Toxicology

/S/ 10/31/00
Stephen G. Hundley, Ph.D.

Concurrences:
HFD-590 / R.Albrecht / DDDir /S/ 11/7/2000
HFD-590 / K.Hastings / TL 11/3/00

Disk:
HFD-590 / K.Hastings

cc:
HFD-590 / Original IND
HFD-590 / Division File
HFD-345
HFD-590 / CSO / J.Fritsch
HFD-590 / MO / R.Roca
HFD-590 / Pharm / S.Hundley
HFD-590 / Chem / G.Holbert
HFD-590 / Micro / P.Dionne
HFD-590 / Biopharm / J.Meyer
HFD-590 / Stat / K.Higgins

APPEARS THIS WAY
ON ORIGINAL

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NDA: 21-154

Clinical and Statistical Review for New Drug Application

December 15, 2000

Clinical and Statistical Review for New Drug Application # 21-154

Drug: Nexium™ (esomeprazole magnesium, formerly H 199/18)
20 mg and 40 mg Delayed-Release Capsules

Applicant's Proposed Indication: *Triple Therapy (NEXIUM™ plus amoxicillin and clarithromycin):* NEXIUM™, in combination with amoxicillin and clarithromycin, is indicated for the treatment of patients with *H. pylori* infection and active or a history of duodenal ulcer disease to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

General Information:

Applicant Name:	AstraZeneca; L.P.
Applicant's Address:	725 Chesterbrook Blvd Wayne, PA 19087
Applicant's Telephone:	(610) 695-1873

Submission/Review Dates:

Date of Submission:	February 28, 2000
Date of Receipt:	February 29, 2000
Date Review Begun:	April 24, 2000
Date Review Completed:	December 15, 2000

Drug Identification:

Generic Name:	Esomeprazole magnesium (formerly H 199/18)
Pharmacologic Category:	substituted benzimidazole (proton pump inhibitor)
Proposed Trade Name:	Nexium™
Chemical Name:	$(C_{17}H_{18}N_3O_3S)_2Mg \times 3\ H_2O$
Molecular Weight:	767.2 daltons
Dosage Form:	20 and 40 mg Delayed-Release Capsules
Route of Administration:	Oral

EXECUTIVE SUMMARY

I. Summary of Clinical Findings

Overview

Generic Name:	Esomeprazole magnesium (formerly H 199/18)
Pharmacologic Category:	substituted benzimidazole (proton pump inhibitor)
Proposed Trade Name:	Nexium™
Dosage Form:	20 and 40 mg Delayed-Release Capsules
Route of Administration:	Oral

Applicant's Proposed Indication: *Triple Therapy (NEXIUM™ plus amoxicillin and clarithromycin):* NEXIUM™, in combination with amoxicillin and clarithromycin, is indicated for the treatment of patients with *H. pylori* infection and active or a history of duodenal ulcer disease to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

The worldwide clinical development program for H 199/18 (esomeprazole) in combination with antimicrobials for the eradication of *H. pylori* includes two Phase I studies (drug-drug interactions) and five Phase III clinical efficacy and safety studies, three of which were conducted in the US.

US Phase III Study 191 is considered primary. Studies 192 and 193 are considered supportive. All three studies used the same design: 38-day, randomized, double blind, parallel group design. Eradication of *H. pylori* was considered the primary endpoint. Duodenal ulcer healing 4 weeks after the end of treatment and upper gastrointestinal symptoms at the end of treatment and 4 weeks after the end of treatment were secondary efficacy parameters. The following treatments were studied for 10 days in a modified factorial design:

US Phase III Studies
Number of Patients Randomized by Study and Treatment Regimen

10-day Treatment	Study Number			Total (%)
	191	192	193	
H 40 mg qd		17	28	37 (7)
H 40 mg qd + C 500 mg bid	251	51		231 (44)
H 40 mg qd + A 1gm bid + C 500 mg bid	264		85	263 (50)
Total (%)	383 (72)	59 (11)	89 (17)	531 (100)

The two non-US Phase III studies (SH-QBE-0019 and SH-QBE-0020) were also double blind, randomized studies. HAC treatment was compared to an active control, OAC (omeprazole/amoxicillin/clarithromycin), and treatments were administered for 7 days. Patients in SH-QBE-0019 had a history of duodenal ulcer disease and the primary endpoint was to estimate the *H. pylori* eradication rates for the two treatment groups. Study SH-QBE-0020 only enrolled patients with active ulcers. The primary endpoint was to estimate duodenal ulcer healing rates for the two treatment groups and the secondary endpoint was to compare eradication rates for the two treatment groups.

Due to differences in the treatment duration, dosing regimen and patient population studied in the US and non-US studies, the efficacy data from the non-US studies will not be discussed. However, the 446 patients who received HAC (n=224 in SH-QBE-0019 and n=222 in SH-QBE-0020) will be reviewed and discussed in the Integrated Summary of Safety (ISS).

A. Efficacy

1. Phase III US Studies

The *H. pylori* eradication rates at 4 weeks post-treatment in US Studies 191, 192, and 193 individually and combined across studies are displayed for the applicant's per-protocol and intention-to-treat analyses in Tables 1 and 2, respectively. The reviewer is in agreement with the applicant's results.

TABLE 1
***H. pylori* Eradication at Day 38 Visit (4 Weeks Post-Treatment)**
Per-Protocol Analysis
US H 199/18 *H. pylori* Studies 191, 192, 193

H. pylori Eradication at 4 Weeks Post-Treatment	HAC	HC	H	Pairwise Treatment Group Comparisons (Using Logistic Regression)
	n/N (%) [95% CI]	n/N (%) [95% CI]	n/N (%) [95% CI]	P-value
Study 191	164/196 (84%) [78%, 89%]	103/187 (55%) [48%, 62%]		HAC vs. HC: $p < 0.001$*
Study 192		22/44 (50%) [35%, 65%]	0/15 (0%) [0%, 22%]	HC vs. H: $p = 0.022$*
Study 193	57/67 (85%) [74%, 93%]		1/22 (5%) [0%, 23%]	HAC vs. H: $p < 0.001$*
All three studies combined [a]	221/263 (84%) [79%, 88%]	125/231 (54%) [48%, 61%]	1/37 (3%) [0%, 14%]	HAC vs HC: $p < 0.001$* HAC vs H: $p < 0.001$* HC vs H: $p < 0.001$*

* Significant difference observed between the treatment groups, ($p < 0.050$).
[a] Test for study by treatment group interaction was not significant, ($p = 0.922$), using logistic regression.

TABLE 2
***H. pylori* Eradication at Day 38 Visit (4 Weeks Post-Treatment)**
Intention-to-Treat Analysis
US H 199/18 *H. pylori* Studies 191, 192, 193

H. pylori Eradication at 4 Weeks Post-Treatment	HAC	HC	H	Pairwise Treatment Group Comparisons (Using Logistic Regression)
	n/N (%) [95% CI]	n/N (%) [95% CI]	n/N (%) [95% CI]	P-value
Study 191	179/233 (77%) [71%, 82%]	112/215 (52%) [45%, 59%]		HAC vs. HC: $p < 0.001$*
Study 192		23/50 (46%) [32%, 61%]	0/16 (0%) [0%, 21%]	HC vs. H: $p = 0.028$*
Study 193	58/74 (78%) [67%, 87%]		1/24 (4%) [0%, 21%]	HAC vs. H: $p < 0.001$*
All three studies combined [a]	237/307 (77%) [72%, 82%]	135/265 (51%) [45%, 57%]	1/40 (3%) [0%, 13%]	HAC vs HC: $p < 0.001$* HAC vs H: $p < 0.001$* HC vs H: $p < 0.001$*

* Significant difference observed between the treatment groups, ($p < 0.050$).
[a] Test for study by treatment group interaction was not significant, ($p = 0.932$), using logistic regression.

The applicant has followed the FDA draft guidance, *Guidance for Industry: Evaluating Clinical Studies of Antimicrobials in the Division of Anti-Infective Drug Products, Draft, February 1997*, in determining efficacy of HAC. According to the document, the following recommendations are made regarding establishment of an efficacy threshold.

- The minimum threshold for efficacy is a lower 95% confidence interval of 60% (using the modified intent-to-treat analysis). However, many factors should be considered in setting this threshold limit. For example; *H. pylori* eradication rates, safety/tolerability levels, rate of emerging resistance, and compliance should all be considered.
- In addition to threshold recommendations, multi-therapy regimens need to include factorial designs, which may demonstrate the contribution of each component to the overall effect.

The *H. pylori* eradication rates for the HAC treatment group satisfy the efficacy threshold recommended in the FDA draft guidance. The 95% confidence intervals for the intention-to-treat eradication rates for the HAC group were (71%, 82%) for Study 191, (67%, 87%) for Study 193, and (72%, 82%) for both studies combined. The lower bounds for all three confidence intervals are above the recommended 60% threshold.

In addition, the *H. pylori* eradication rates for the HAC treatment group were significantly higher than both the HC and H treatment groups, demonstrating the superiority of HAC over the other two regimens and also the positive contribution of amoxicillin to the HAC regimen.

2. Comparison With Other FDA-approved PPI-based Triple Therapy Regimens

Omeprazole and lansoprazole are proton pump inhibitors (PPIs) that are approved in combination with two antibiotics for eradication of *H. pylori*.

- OAC (omeprazole/amoxicillin/clarithromycin)
- LAC (lansoprazole/amoxicillin/clarithromycin)

The clinical development programs for these regimens were similar to that of HAC. All programs enrolled *H. pylori*-positive patients with either an active ulcer or history of ulcer disease. Eradication was the primary endpoint in all studies. The treatment duration of the PPI varied between development programs. In the OAC regimen, the use of omeprazole was continued (at a reduced dose) beyond the duration of eradication therapy for a total duration of 4 weeks. The HAC and LAC regimens did not continue the PPI beyond the initial 10 days of treatment.

As seen in the table below, the eradication rates achieved at 4 weeks post-treatment with HAC therapy appear comparable to those observed with the other approved proton pump inhibitor (PPI)-based triple therapies:

H. pylori Eradication at 4 Weeks Post-Treatment - Comparison of Esomeprazole (H199/18), Omeprazole, and Lansoprazole Triple Therapies

Analysis	N (%) [95% CI]					
	HAC		*OAC**			*LAC*Ψ*
	Study 191	Study 193	Study 126	Study 127	Study M96-446	M95-399
ITT	233 (77%) [71%, 82%]	74 (78%) [67%, 87%]	80 (69%) [57%, 79%]	73 (77%) [61%, 82%]	84 (83%) [74 %, 91%]	135 (81%) [74%, 88%]
PP	196 (84%) [78%, 89%]	67 (85%) [74%, 93%]	64 (77%) [64%, 86%]	65 (78%) [67%, 88%]	69 (90%) [80 %, 96%]	123 (84%) [76%, 90%]

* Omeprazole 20 mg BID + amoxicillin 1gm BID + Clarithromycin 500 mg BID x 10 days, then omeprazole 20 mg QD for an additional 18 days in patients with an active ulcer present at the initiation of therapy for ulcer healing and symptom relief. M96-446 was an inactive DU study, therefore omeprazole was used for a duration of 10 days in all patients.

Ψ Lansoprazole 30 mg BID + amoxicillin 1 gm BID + clarithromycin 500 mg BID x 10 days

B. **Safety - US Phase III studies**

In the US Phase III studies, there were no clinically meaningful differences between the HAC and HC groups in the incidence of any AE (54.3% and 55.5%, respectively). These results suggest that the addition of amoxicillin to the HC regimen does not lead to an increased risk of adverse side effects. In contrast, the percentage of patients who reported AEs was generally lower for patients who received H alone (46.7%) compared to those who received HAC or HC. This lower rate was observed specifically for abdominal pain, diarrhea, flatulence, nausea, esophagitis, dizziness, headache, and taste perversion. Dizziness, headache, and abnormal taste have been previously associated with clarithromycin.

The increased incidence of AEs in the HAC and HC groups, as compared to the H group may be due to the increased exposure to H 199/18 that occurs with co-administration of clarithromycin. However, it is more likely to be a direct result of the antibiotic component(s)

XI. Dosing and Administration Issues

Esomeprazole was studied at a dose of 40 mg once daily for the eradication of *H. pylori*. In studies for other GI indications (healing of erosive esophagitis, maintenance of healing of erosive esophagitis, and treatment of symptomatic GERD), a dose of 20 mg was found to be equivalent to 40 mg in terms of the degree of acid suppression.

Clinical Reviewer's Comment: Based on MO's review for NDA 21-153.

Use of higher dose for eradication of *H. pylori* is consistent with how the other approved PPIs are labeled. The *H. pylori* indicated doses of omeprazole and lansoprazole are higher than the traditional GI indications, excluding ——— for purposes of this discussion. Omeprazole is dosed 20 mg twice daily in combination with amoxicillin and clarithromycin and 40 mg once daily in combination with clarithromycin for eradication of *H. pylori*. The dose of omeprazole is 20-40 mg once daily for other GI indications (see table below). Lansoprazole is dosed 30 mg three times daily in combination with amoxicillin and 30 mg twice daily in combination with amoxicillin and clarithromycin for eradication of *H. pylori*. The dose of lansoprazole is 15-30 mg once daily for other GI indications (see table below).

Approved Doses of Omeprazole and Lansoprazole for Various GI Indications*

Omeprazole		Lansoprazole	
20 mg QD	40 mg QD	15 mg QD	30 mg QD
Treatment of active duodenal ulcer	Treatment of active gastric ulcer	Treatment of active duodenal ulcer and maintenance of healing	Treatment of active gastric ulcer
Treatment of symptomatic GERD and erosive esophagitis		Treatment of symptomatic GERD	Treatment of erosive esophagitis
Maintenance of healing of erosive esophagitis		Maintenance of healing of erosive esophagitis	

*excluding ———

The mechanism of action of PPIs in the treatment of *H. pylori* is believed to be more complex than just inhibition of acid suppression.

- Co-administration of a PPI with antimicrobials appears to enhance the action of the antimicrobials by several possible mechanisms. PPIs have direct antimicrobial activity against *H. pylori in vitro* by inhibiting bacterial urease. Inhibition of this enzyme can decrease the bacteria's ability to colonize the gastric mucosa.

- The decrease in gastric acidity produced by PPIs may reduce the degradation of acid-labile antimicrobials, such as amoxicillin, and also enhance eradication of the organism. In addition, an increased pH is a less suitable environment for growth of *H. pylori*.

- Finally, *H. pylori* affects the magnitude of acid inhibition produced by PPIs. Omeprazole has been shown to produce greater acid suppression in infected subjects than in uninfected controls and duodenal ulcer patients.

In summary, approval of the 40 mg dose of esomeprazole in combination with antimicrobials for eradication of *H. pylori* is consistent with other approved PPIs for this indication and appears warranted based on what is known of the pharmacology of this infection.

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NDA: 21-153, 21-154

Approvable Letters for 21-153, 21-154

December 15, 2000

Excerpted Pages from: http://www.fda.gov/cder/foi/nda/2001/21154_Nexium_Approv[1].pdf

Downloaded: October 4, 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-153/ 21-154

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-153
NDA 21-154

DEC 15

AstraZeneca LP
Attention: Gary P. Horowitz, Ph.D.
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Dr. Horowitz:

Please refer to your new drug application (NDA 21-153) dated December 3, 1999, received December 3, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nexium (esomeprazole magnesium) Delayed-Release Capsules.

We acknowledge receipt of your submissions dated December 13 and December 22, 1999; and January 19, January 31, March 3, March 17, April 3, April 27, June 1, June 5, June 23, July 17, August 2, August 4, August 14, August 16, August 25, October 6, October 13, October 16, October 19, and November 20, 2000. Your submission of October 16, 2000 (together with your submission of October 6, 2000) constituted a complete response to our October 3, 2000 action letter.

This application provides for the following proposed indications: 1) healing of erosive esophagitis; 2) maintenance of healing of erosive esophagitis; and 3) treatment of symptomatic gastroesophageal reflux disease.

Please also refer to your new drug application (NDA 21-154) dated February 28, 2000, received February 28, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nexium (esomeprazole magnesium) Delayed-Release Capsules.

We acknowledge receipt of your submissions dated April 12, June 6, June 12, and November 17, 2000.

This application provides for the use of omeprazole magnesium in combination with clarithromycin and amoxicillin for the eradication of *Helicobacter pylori* in patients with duodenal ulcer disease or a history of duodenal ulcer disease.

We have completed the review of these applications as amended, and they are approvable. Before these NDAs may be approved, however, it will be necessary for you to submit revised draft labeling for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert).

We also have the following comments regarding the container labels and expiration date for the drug product:

1. All proposals regarding the package labels included in your November 20, 2000 amendment to NDA 21-153 are acceptable.

2. The stability data submitted support an expiration date of 24 months.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Maria R. Walsh, M.S., Project Manager, at (301) 443-8017.

Sincerely,

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Mark J. Goldberger, M.D., M.P.H.
Director
Division of Special Pathogen
and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure

APPEARS THIS WAY
ON ORIGINAL

Lilia Talarico
12/15/00 04:05:16 PM

Renata Albrecht
12/15/00 04:14:14 PM
for Mark Goldberger, M.D., M.P.H.

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ON ORIGINAL

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NDA: 21-153

Memorandum of Director, Division of Gastrointestinal and Coagulation Drug Products

February 20, 2001

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 20, 2001

FROM: Director, Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Nexium (esomeprazole magnesium H199/18)

TO: NDA 21-153

Nexium (esomeprazole magnesium, H199/18) is the s-enantomer of the proton pump inhibitor (PPI) omeprazole. As the parent compound, esomeprazole suppresses gastric acid secretion through dose-related inhibition of the H^+/K^+- ATPase enzyme system.

Based on the claim that esomeprazole has a metabolic profile that may differ from that of omeprazole, the sponsor has performed the clinical development of this enantomer for gastroesophageal reflux disease (GERD), including healing of erosive esophagitis (EE), maintenance of healing of EE and treatment of symptomatic GERD in addition to eradication of H. pylori to reduce the risk of duodenal ulcer recurrence.

On December 3, 1999, the sponsor submitted an NDA (NDA 21-153) for the marketing approval of Nexium for the following indications:

1) healing of erosive esophagitis,
2) maintenance of healing of EE,
3) treatment of symptomatic gastroesophageal reflux disease.

NDA 21-153 was reviewed by Dr. Gallo-Torres with the recommendation that esomeprazole be approvable for the above indications with labeling changes including the recommendation for the dose regimen of 20 mg/qd for the for the indication of healing of EE.

On October 16, 1999, the sponsor responded to the approvable letter with the submission of a document that addressed the difference in the metabolic profile of esomeprazole and omeprazole and the efficacy data from the clinical trials of healing of EE to support the sponsor's recommendation for the 40 mg/qd dose regimen. A revised labeling was submitted.

This review will address only the esomeprazole indication for healing and maintenance of EE and the clinical trials submitted in the NDA to support the sponsor's recommendation

of the dose regimen. Dr. Gallo-Torres's medical review and the Biopharm review can be referenced for information regarding the PK and PD characteristics of esomeprazole.

The clinical development of esomeprazole was initiated in 1997 when the sponsor submitted three study protocols for the acute healing of EE. Study 172 was a double blinded, three arm study that compared esomeprazole 40 and 20 mg qd to omeprazole 20 mg qd for 8 weeks. Study 173 compared esomeprazole 40 mg/qd to omeprazole 20 mg/qd for 8 weeks. At completion of study 172, responders were randomized to a four arm study of maintenance therapy with esomeprazole 10, 20 or 40 mg/qd or placebo for 6 months. Study 174 compared esomeprazole 20 mg/qd to omeprazole 20 mg/qd for 8 weeks followed by open-label maintenance therapy with esomeprazole 40 mg/qd for 12 months.

Because the healing rates for omeprazole 20 mg/qd in studies 173 and 174 were higher than the anticipated rate of 75% (90% and 88% respectively) and not significantly different from esomeprazole 40 mg/qd , a fourth study (study 222) was subsequently designed to demonstrate statistically significant difference in healing rates for esomeprazole 40 mg/qd and omeprazole 20 mg/qd. The study was powered to show a 5% difference in healing rates between the two treatment groups.

All four clinical trials were considered to be pivotal.

The results of the four trials are summarized in the following tables.

Erosive Esophagitis Healing Rate (Life-Table Analysis)

Study	No. of Patients	Treatment Group	Week 4 of therapy	Week 8	Significance *
#172	654 656 650	Esomeprazole 40 mg Esomeprazole 20 mg Omeprazole 20 mg	75.9% 70.5% 64.7%	94.1% 89.9% 86.9%	P<0.001 P<0.05%
#173	576 572	Esomeprazole 40 mg Omeprazole 20 mg	71.5% 68.6%	92.2% 89.9%	NS
#174	588 588	Esomeprazole 20 mg Omeprazole 20 mg	68.7% 69.5%	90.6% 88.3%	NS
#222	1216 1209	Esomeprazole 40 mg Omeprazole 20 mg	81.7% 68.7%	93.7% 84.2%	P<0.001

* Compared to Omeprazole 20 mg
NS=not significant (p>0.05)

Efficacy for healing of EE was established at both dose regimens of esomeprazole 40 mg/qd and 20 mg/qd compared to omeprazole 20 mg/qd. In two studies, esomeprazole 40 mg/qd resulted in statistically higher healing rates than omeprazole 20 mg/qd, however, esomeprazole 20 mg/qd was not significantly different from omeprazole 20 mg/qd.

Analyses of the secondary endpoints of sustained resolution of heartburn by week 4 showed greater rate of responders for the esomeprazole 40 mg/qd in two studies that

compared these regimens to omeprazole 20 mg/qd. No difference was noted between the esomeprazole 20 mg/qd and the omeprazole 20 mg/qd treatment groups.

Since the difference between the esomeprazole 20 mg/qd and the omeprazole 20 mg/qd observed in study 172 was not reproduced in study 174, the observed differences in healing rates and symptom relief for esomeprazole 40 mg and omeprazole 20 mg may reflect differences in dose rather than metabolic or pharmacologic differences. No clinical comparison of 40 mg of esomeprazole with 40 mg of omeprazole were performed to quantify the effect of metabolic differences of this dose.

In addition to EE, esomeprazole has been evaluated for the treatment of symptomatic GERD in five clinical trials, two placebo-controlled, and three with omeprazole 20 mg/qs as comparator. Esomeprazole at 20 mg/qd and 40 mg/qd was statistically significantly superior to placebo. No significant difference was noted between the 20 nad 40 mg/qd doses of esomeprazole and between 40 or 20 mg/qd of esomeprazole and 20 mg/qd of omeprazole.

The efficacy of esomeprazole for maintenance of healing of EE was evaluated in two double-blind clinical trials that enrolled patients from study 172 with healed EE. Three daily dose levels of esomeprazole of 40 mg, 20 mg and 10 mg to placebo for 6 months. All three dose regimens of esomeprazole were significantly superior to placebo (p-value <0.001) for the proportion of patients with healed EE through the 6 months of treatment. No significant difference was noted for the esomeprazole 40 and 20 mg/qd.

No differences in safety among the treatment regimens of esomeprazole 40, 20 mg/qd or omeprazole 20 mg/qd were observed.

In conclusion, the results of the studies have demonstrated that esomeprazole is safe and effective for the healing of EE. The results of the clinical trials support both esomeprazole regimens of 20 and 40 mg/qd for the healing of EE. Both dose regimens are recommended for approval, but there is no information on when to choose one over the other.

Labeling revisions agreed upon by the Agency and by the sponsor were finalized on 2-12-2001.

APPEARS THIS WAY
ON ORIGINAL

/s/

Lilia Talarico
2/20/01 04:34:17 PM
MEDICAL OFFICER

APPEARS THIS WAY
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NDA: 21-153, 21-154

Approved Labeling

February, 2001

Excerpted pages from: www.fda.gov/cder/foi/label/2001/21153lbl.pdf

Downloaded: October 4, 2005

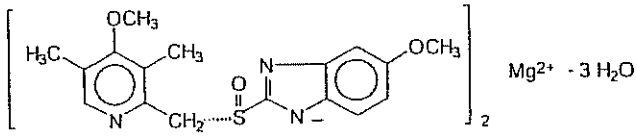
NEXIUM™

(esomeprazole magnesium)
DELAYED-RELEASE CAPSULES

Rx only

DESCRIPTION

The active ingredient in NEXIUM™ (esomeprazole magnesium) Delayed-Release Capsules is bis(5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole-1-yl) magnesium trihydrate, a compound that inhibits gastric acid secretion. Esomeprazole is the S-isomer of omeprazole, which is a mixture of the S- and R- isomers. Its empirical formula is $(C_{17}H_{18}N_3O_3S)_2Mg \times 3\ H_2O$ with molecular weight of 767.2 as a trihydrate and 713.1 on an anhydrous basis. The structural formula is:



The magnesium salt is a white to slightly colored crystalline powder. It contains 3 moles of water of solvation and is slightly soluble in water.
The stability of esomeprazole magnesium is a function of pH; it rapidly degrades in acidic media, but it has acceptable stability under alkaline conditions. At pH 6.8 (buffer), the half-life of the magnesium salt is about 19 hours at 25°C and about 8 hours at 37°C.

NEXIUM is supplied as Delayed-Release Capsules for oral administration. Each delayed-release capsule contains 20 mg or 40 mg of esomeprazole (present as 22.3 mg or 44.5 mg esomeprazole magnesium trihydrate) in the form of enteric-coated pellets with the following inactive ingredients: glyceryl monostearate 40-50, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, methacrylic acid copolymer type C, polysorbate 80, sugar spheres, talc, and triethyl citrate. The capsule shells have the following inactive ingredients: gelatin, FD&C Blue #1, FD&C Red #40, D&C Red #28, titanium dioxide, shellac, ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, sodium hydroxide, polyvinyl pyrrolidone, and D&C Yellow #10.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption
NEXIUM Delayed-Release Capsules contain an enteric-coated pellet formulation of esomeprazole magnesium. After oral administration peak plasma levels (C_{max}) occur at approximately 1.5 hours (T_{max}). The C_{max} increases proportionally when the dose is increased, and there is a three-fold increase in the area under the plasma concentration-time curve (AUC) from 20 to 40 mg. At repeated once-daily dosing with 40 mg, the systemic bioavailability is approximately 90% compared to 64% after a single dose of 40 mg. The mean exposure (AUC) to esomeprazole increases from 4.32 µmol*hr/L on day 1 to

11.2 µmol*hr/L on day 5 after 40 mg once daily dosing.
The AUC after administration of a single 40 mg dose of esomeprazole is decreased by 33-53% after food intake compared to fasting conditions. Esomeprazole should be taken at least one hour before meals.

The pharmacokinetic profile of esomeprazole was determined in 36 patients with symptomatic gastroesophageal reflux disease following repeated once daily administration of 20 mg and 40 mg capsules of NEXIUM over a period of five days. The results are shown in the following table:

Pharmacokinetic Parameters of NEXIUM Following Oral Dosing for 5 days

Parameter	NEXIUM 40 mg	NEXIUM 20 mg
AUC (µmol*h/L)	12.6	4.2
Coefficient of variation	42%	59%
C_{max} (µmol/L)	4.7	2.1
T_{max} (h)	1.6	1.6
$t_{1/2}$ (h)	1.5	1.2

Values represent the geometric mean, except the T_{max} which is the arithmetic mean.

Distribution
Esomeprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 2-20 µmol/L. The apparent volume of distribution at steady state in healthy volunteers is approximately 16 L.

Metabolism
Esomeprazole is extensively metabolized in the liver by the cytochrome P450 (CYP) enzyme system. The metabolites of esomeprazole lack antisecretory activity. The major part of esomeprazole's metabolism is dependent upon the CYP2C19 isoenzyme, which forms the hydroxy and desmethyl metabolites. The remaining amount is dependent on CYP3A4 which forms the sulphone metabolite. CYP2C19 isoenzyme exhibits polymorphism in the metabolism of esomeprazole, since some 3% of Caucasians and 15-20% of Asians lack CYP2C19 and are termed Poor metabolizers. At steady state, the ratio of AUC in Poor metabolizers to AUC in the rest of the population (Extensive metabolizers) is approximately 2.

Following administration of equimolar doses, the S- and R-isomers are metabolized differently by the liver, resulting in higher plasma levels of the S- than of the R-isomer.

Excretion
The plasma elimination half-life of esomeprazole is approximately 1-1.5 hours. Less than 1% of parent drug is excreted in the urine. Approximately 80% of an oral dose of esomeprazole is excreted as inactive metabolites in the urine, and the remainder is found as inactive metabolites in the feces.

Special Populations

Geriatric
The AUC and C_{max} values were slightly higher (25% and 18%, respectively) in the elderly as compared to younger subjects at steady state. Dosage adjustment based on age is not necessary.

Pediatric
The pharmacokinetics of esomeprazole have not been studied in patients < 18 years of age.

Gender
The AUC and C_{max} values were slightly higher (13%) in females than in males at steady state. Dosage adjustment based on gender is not necessary.

Hepatic Insufficiency
The steady state pharmacokinetics of esomeprazole obtained after administration of 40 mg once daily to 4 patients each with mild (Child Pugh A), moderate (Child Pugh Class B), and severe (Child Pugh Class C) liver insufficiency were compared to those obtained in 36 male and female GERD patients with normal liver function. In patients with mild and moderate hepatic insufficiency, the AUCs were within the range that could be expected in patients with normal liver function. In patients with severe hepatic insufficiency the AUCs were 2 to 3 times higher than in the patients with normal liver function. No dosage adjustment is recommended for patients with mild to moderate hepatic insufficiency (Child Pugh Classes A and B). However, in patients with severe hepatic insufficiency (Child Pugh Class C) a dose of 20 mg once daily should not be exceeded (See **DOSAGE AND ADMINISTRATION**).

Renal Insufficiency
The pharmacokinetics of esomeprazole in patients with renal impairment are not expected to be altered relative to healthy volunteers as less than 1% of esomeprazole is excreted unchanged in urine.

Pharmacokinetics: Combination Therapy with Antimicrobials
Esomeprazole magnesium 40 mg once daily was given in combination with clarithromycin 500 mg twice daily and amoxicillin 1000 mg twice daily for 7 days to 17 healthy male and female subjects. The mean steady state AUC and C_{max} of esomeprazole increased by 70% and 18%, respectively during triple combination therapy compared to treatment with esomeprazole alone. The observed increase in esomeprazole exposure during co-administration with clarithromycin and amoxicillin is not expected to produce significant safety concerns.

The pharmacokinetic parameters for clarithromycin and amoxicillin were similar during triple combination therapy and administration of each drug alone. However, the mean AUC and C_{max} for 14-hydroxyclarithromycin increased by 19% and 22%, respectively, during triple combination therapy compared to treatment with clarithromycin alone. This increase in exposure to 14-hydroxyclarithromycin is not considered to be clinically significant.

Pharmacodynamics
Mechanism of Action
Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H^+/K^+-ATPase in the gastric parietal cell. The S- and R-isomers are protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, the achiral sulphenamide. By acting specifically on the proton pump, esomeprazole blocks the final step in acid production, thus reducing gastric acidity. This effect is dose-related up to a daily dose of 20 to 40 mg and leads to inhibition of gastric acid secretion.

Antisecretory Activity

The effect of esomeprazole on intragastric pH was determined in patients with symptomatic gastroesophageal reflux disease in two separate studies. In the first study of 36 patients, NEXIUM 40 mg and 20 mg capsules were administered over 5 days. The results are shown in the following table:

Effect on Intragastric pH On Day 5 (N=36)

Parameter	NEXIUM 40 mg	NEXIUM 20 mg
% Time Gastric pH >4[†] (Hours)	70%* (16.8 h)	53% (12.7 h)
Coefficient of variation	26%	37%
Median 24 Hour pH	4.9*	4.1
Coefficient of variation	16%	27%

[†] Gastric pH was measured over a 24-hour period
*p< 0.01 NEXIUM 40 mg vs NEXIUM 20 mg

In a second study, the effect on intragastric pH of NEXIUM 40 mg administered once daily over a five day period was similar to the first study, (% time with pH>4 was 68% or 16.3 hours).

Serum Gastrin Effects

The effect of NEXIUM on serum gastrin concentrations was evaluated in approximately 2,700 patients in clinical trials up to 8 weeks and in over 1,300 patients for up to 6-12 months. The mean fasting gastrin level increased in a dose-related manner. This increase reached a plateau within two to three months of therapy and returned to baseline levels within four weeks after discontinuation of therapy.

Enterochromaffin-like (ECL) Cell Effects

In 24-month carcinogenicity studies of omeprazole in rats, a dose-related significant occurrence of gastric ECL cell carcinoid tumors and ECL cell hyperplasia was observed in both male and female animals (see **PRECAUTIONS,** Carcinogenesis, Mutagenesis, Impairment of Fertility). Carcinoid tumors have also been observed in rats subjected to fundectomy or long-term treatment with other proton pump inhibitors or high doses of H_2-receptor antagonists.

Human gastric biopsy specimens have been obtained from more than 3,000 patients treated with omeprazole in long-term clinical trials. The incidence of ECL cell hyperplasia in these studies increased with time; however, no case of ECL cell carcinoids, dysplasia, or neoplasia has been found in these patients.

In over 1,000 patients treated with NEXIUM (10, 20 or 40 mg/day) up to 6-12 months, the prevalence of ECL cell hyperplasia increased with time and dose. No patient developed ECL cell carcinoids, dysplasia, or neoplasia in the gastric mucosa.

Endocrine Effects

NEXIUM had no effect on thyroid function when given in oral doses of 20 or 40 mg for 4 weeks. Other effects of NEXIUM on the endocrine system were assessed using omeprazole studies. Omeprazole

given in oral doses of 30 or 40 mg for 2 to 4 weeks had no effect on carbohydrate metabolism, circulating levels of parathyroid hormone, cortisol, estradiol, testosterone, prolactin, cholecystokinin or secretin.

Microbiology

Esomeprazole magnesium, amoxicillin and clarithromycin triple therapy has been shown to be active against most strains of *Helicobacter pylori (H. pylori) in vitro* and in clinical infections as described in the **Clinical Studies** and **INDICATIONS AND USAGE** sections.

Helicobacter

Helicobacter pylori

Susceptibility testing of *H. pylori* isolates was performed for amoxicillin and clarithromycin using agar dilution methodology, and minimum inhibitory concentrations (MICs) were determined.

Pretreatment Resistance

Clarithromycin pretreatment resistance rate (MIC $\geq$ 1 µg/mL) to *H. pylori* was 15% (66/445) at baseline in all treatment groups combined. A total of > 99% (394/395) of patients had *H. pylori* isolates which were considered to be susceptible (MIC $\leq$ 0.25 µg/mL) to amoxicillin at baseline. One patient had a baseline
H. pylori isolate with an amoxicillin MIC = 0.5 µg /mL.

Clarithromycin Susceptibility Test Results and Clinical/Bacteriologic Outcomes

The baseline *H. pylori* clarithromycin susceptibility results and the *H. pylori* eradication results at the Day 38 visit are shown in the table below:

Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes[a] for Triple Therapy - (Esomeprazole magnesium 40 mg once daily/amoxicillin 1000 mg twice daily/clarithromycin 500 mg twice daily for 10 days)

Clarithromycin Pretreatment Results	*H. pylori* negative (Eradicated)	*H. pylori* positive (Not Eradicated) Post-treatment susceptibility results			
		S[b]	I[b]	R[b]	No MIC
Susceptible[b] 182	162	4	0	2	14
Intermediate[b] 1	1	0	0	0	0
Resistant[b] 29	13	1	0	13	2

[a]Includes only patients with pretreatment and post-treatment clarithromycin susceptibility test results
[b]Susceptible (S) MIC ≤ 0.25 µg/mL, Intermediate (I) MIC =0.5 µg/mL, Resistant (R) MIC ≥ 1.0 µg /mL

Patients not eradicated of *H. pylori* following esomeprazole magnesium/amoxicillin/clarithromycin triple therapy will likely have clarithromycin resistant *H. pylori* isolates. Therefore, clarithromycin susceptibility testing should be done, when possible. Patients with clarithromycin resistant *H. pylori* should not be re-treated with a clarithromycin-containing regimen.

Amoxicillin Susceptibility Test Results and Clinical/Bacteriological Outcomes
In the esomeprazole magnesium/amoxicillin/clarithromycin clinical trials, 83% (176/212) of the patients in the esomeprazole magnesium/amoxicillin/clarithromycin treatment group who had pretreatment amoxicillin susceptible MICs (≤ 0.25 µg/mL) were eradicated of *H. pylori*, and 17% (36/212) were not eradicated of H. *pylori*. Of the 36 patients who were not eradicated of *H. pylori* on triple therapy, 16 had no post-treatment susceptibility test results and 20 had post-treatment *H. pylori* isolates with amoxicillin susceptible MICs. Fifteen of the patients who were not eradicated of *H. pylori* on triple therapy also had post-treatment *H. pylori* isolates with clarithromycin resistant MICs. There were no patients with *H. pylori* isolates who developed treatment emergent resistance to amoxicillin.

Susceptibility Test for Helicobacter pylori
The reference methodology for susceptibility testing of *H. pylori* is agar dilution MICs. One to three microliters of an inoculum equivalent to a No.2 McFarland standard (1×10^7 - 1×10^8 CFU/mL for *H. pylori*) are inoculated directly onto freshly prepared antimicrobial containing Mueller-Hinton agar plates with 5% aged defibrinated sheep blood (≥2 weeks old). The agar dilution plates are incubated at 35°C in a microaerobic environment produced by a gas generating system suitable for *Campylobacter*. After 3 days of incubation, the MICs are recorded as the lowest concentration of antimicrobial agent required to inhibit growth of the organism. The clarithromycin and amoxicillin MIC values should be interpreted according to the following criteria:

Clarithromycin MIC (µg/mL) [a]	Interpretation	
≤ 0.25	Susceptible	(S)
0.5	Intermediate	(I)
≥1.0	Resistant	(R)

Amoxicillin MIC (µg/mL) [a,b]	Interpretation	
≤ 0.25	Susceptible	(S)

[a] These are breakpoints for the agar dilution methodology and they should not be used to interpret results obtained using alternative methods.

[b] There were not enough organisms with MICs > 0.25 µg /mL to determine a resistance breakpoint.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard clarithromycin and amoxicillin powders should provide the following MIC values:

Microorganism	Antimicrobial Agent	MIC (µg/mL) [a]
H. pylori ATCC 43504	Clarithromycin	0.016 – 0.12 (µg/mL)
H. pylori ATCC 43504	Amoxicillin	0.016 – 0.12 (µg/mL)

[a] These are quality control ranges for the agar dilution methodology and they should not be used to control test results obtained using alternative methods.

Clinical Studies

Healing of Erosive Esophagitis

The healing rates of NEXIUM 40 mg, NEXIUM 20 mg, and omeprazole 20 mg (the approved dose for this indication) were evaluated in patients with endoscopically diagnosed erosive esophagitis in four multicenter, double-blind, randomized studies. The healing rates at weeks 4 and 8 were evaluated and are shown in the table below:

Erosive Esophagitis Healing Rate (Life-Table Analysis)

Study	No. of Patients	Treatment Groups	Week 4	Week 8	Significance Level *
1	588	NEXIUM 20 mg	68.7%	90.6%	N.S.
	588	Omeprazole 20 mg	69.5%	88.3%	
2	654	NEXIUM 40 mg	75.9%	94.1%	$p < 0.001$
	656	NEXIUM 20 mg	70.5%	89.9%	$p < 0.05$
	650	Omeprazole 20 mg	64.7%	86.9%	
3	576	NEXIUM 40 mg	71.5%	92.2%	N.S.
	572	Omeprazole 20 mg	68.6%	89.8%	
4	1216	NEXIUM 40 mg	81.7%	93.7%	$p < 0.001$
	1209	Omeprazole 20 mg	68.7%	84.2%	

*log-rank test vs omeprazole 20 mg
N.S. = not significant (p > 0.05).

In these same studies of patients with erosive esophagitis, sustained heartburn resolution and time to sustained heartburn resolution were evaluated and are shown in the table below:

Sustained Resolution‡ of Heartburn (Erosive Esophagitis Patients)

			Cumulative Percent# with Sustained Resolution		
Study	No. of Patients	Treatment Groups	Day 14	Day 28	Significance Level *
1	573	NEXIUM 20 mg	64.3%	72.7%	N.S.
	555	Omeprazole 20 mg	64.1%	70.9%	
2	621	NEXIUM 40 mg	64.8%	74.2%	p <0.001
	620	NEXIUM 20 mg	62.9%	70.1%	N.S.
	626	Omeprazole 20 mg	56.5%	66.6%	
3	568	NEXIUM 40 mg	65.4%	73.9%	N.S.
	551	Omeprazole 20 mg	65.5%	73.1%	
4	1187	NEXIUM 40 mg	67.6%	75.1%	p <0.001
	1188	Omeprazole 20 mg	62.5%	70.8%	

‡Defined as 7 consecutive days with no heartburn reported in daily patient diary.
#Defined as the cumulative proportion of patients who have reached the start of sustained resolution
*log-rank test vs omeprazole 20 mg
N.S. = not significant (p > 0.05).

In these four studies, the range of median days to the start of sustained resolution (defined as 7 consecutive days with no heartburn) was 5 days for NEXIUM 40 mg, 7-8 days for NEXIUM 20 mg and 7-9 days for omeprazole 20 mg.

There are no comparisons of 40 mg of NEXIUM with 40 mg of omeprazole in clinical trials assessing either healing or symptomatic relief of erosive esophagitis.

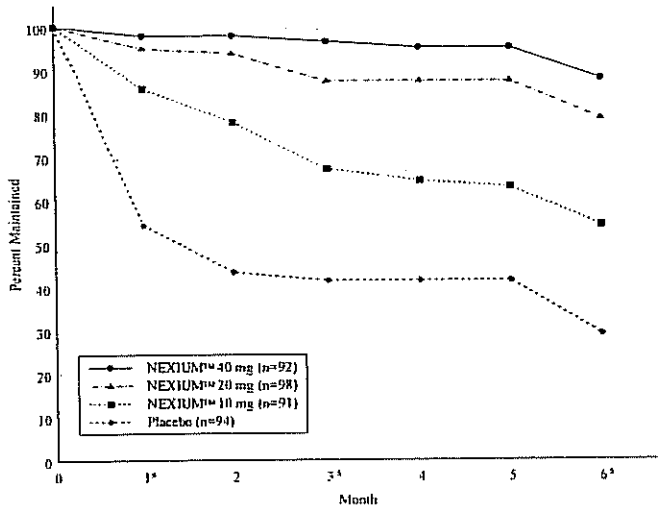
Long-Term Maintenance of Healing of Erosive Esophagitis

Two multicenter, randomized, double-blind placebo-controlled 4-arm trials were conducted in patients with endoscopically confirmed, healed erosive esophagitis to evaluate NEXIUM 40 mg (n=174), 20 mg (n=180), 10 mg (n= 168) or placebo (n=171) once daily over six months of treatment.

No additional clinical benefit was seen with NEXIUM 40 mg over NEXIUM 20 mg.

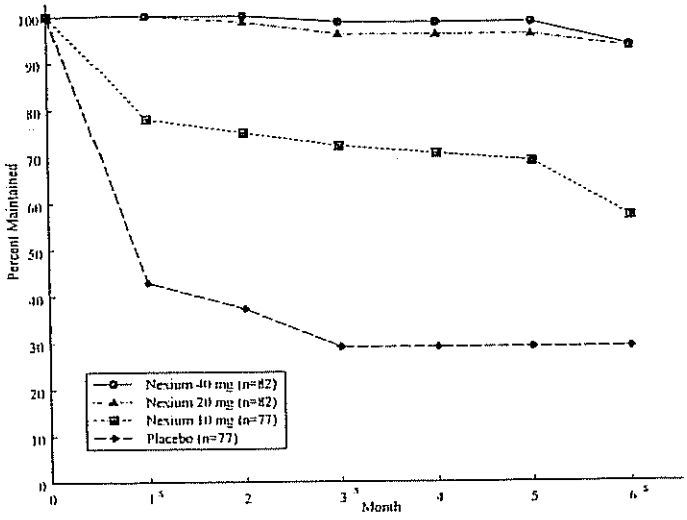
The percentage of patients that maintained healing of erosive esophagitis at the various time points are shown in the figures below:

Maintenance of Healing Rates by Month (Study 177)



s= scheduled visit

Maintenance of Healing Rates by Month (Study 178)



s= scheduled visit

Patients remained in remission significantly longer and the number of recurrences of erosive esophagitis was significantly less in patients treated with NEXIUM compared to placebo.

In both studies, the proportion of patients on NEXIUM who remained in remission and were free of heartburn and other GERD symptoms was well differentiated from placebo.

In a third multicenter open label study of 808 patients treated for 12 months with NEXIUM 40 mg, the percentage of patients that maintained healing of erosive esophagitis was 93.7% for six months and 89.4% for one year.

Symptomatic Gastroesophageal Reflux Disease (GERD)

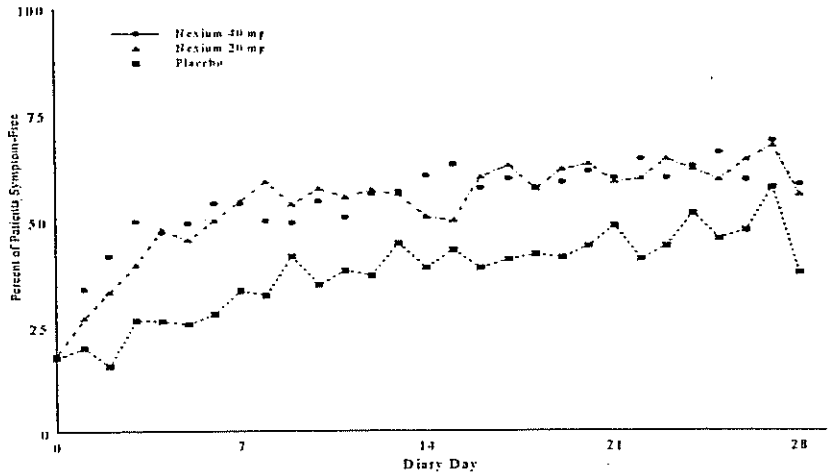
Two multicenter, randomized, double-blind, placebo-controlled studies were conducted in a total of 717 patients comparing four weeks of treatment with NEXIUM 20 mg or 40 mg once daily versus placebo for resolution of GERD symptoms. Patients had ≥ 6-month history of heartburn episodes, no erosive esophagitis by endoscopy, and heartburn on at least four of the seven days immediately preceding randomization.

The percentage of patients that were symptom-free of heartburn was significantly higher in the NEXIUM groups compared to placebo at all follow-up visits (Weeks 1, 2, and 4).

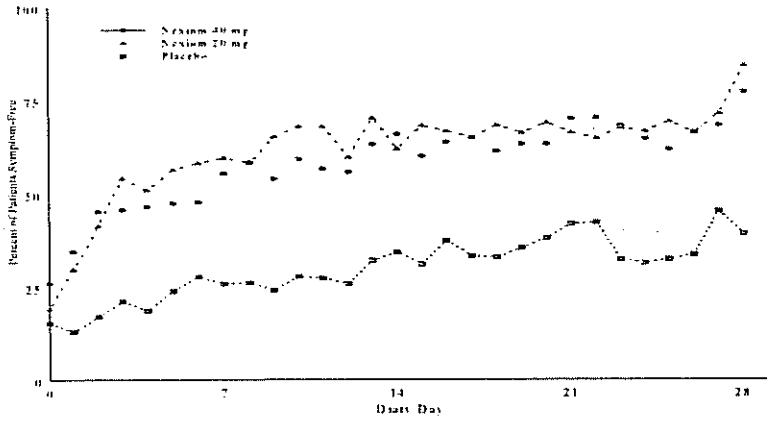
No additional clinical benefit was seen with NEXIUM 40 mg over NEXIUM 20 mg.

The percent of patients symptom-free of heartburn by day are shown in the figures below:

Percent of Patients Symptom-Free of Heartburn by Day
(Study 225)



Percent of Patients Symptom-Free of Heartburn by Day
(Study 226)



In three European symptomatic GERD trials, NEXIUM 20 mg and 40 mg and omeprazole 20 mg were evaluated. No significant treatment related differences were seen.

Helicobacter pylori *(H. pylori) Eradication in Patients with Duodenal Ulcer Disease*
Triple Therapy (NEXIUM/amoxicillin/clarithromycin): Two multicenter, randomized, double-blind studies were conducted using a 10 day treatment regimen. The first study (191) compared NEXIUM 40 mg once daily in combination with amoxicillin 1000 mg twice daily and clarithromycin 500 mg twice daily to NEXIUM 40 mg once daily plus clarithromycin 500 mg twice daily. The second study (193) compared NEXIUM 40 mg once daily in combination with amoxicillin 1000 mg twice daily and clarithromycin 500 mg twice daily to NEXIUM 40 mg once daily. *H. pylori* eradication rates, defined as at least two negative tests and no positive tests from CLOtest®, histology and/or culture, at 4 weeks post-therapy were significantly higher in the NEXIUM plus amoxicillin and clarithromycin group than in the NEXIUM plus clarithromycin or NEXIUM alone group. The results are shown in the following table:

H. pylori Eradication Rates at 4 Weeks after 10 Day Treatment Regimen
% of Patients Cured
[95% Confidence Interval]
(Number of patients)

Study	Treatment Group	Per-Protocol[†]	Intent-to-Treat [‡]
191	NEXIUM plus amoxicillin and clarithromycin	84%* [78, 89] (n=196)	77%* [71, 82] (n=233)
	NEXIUM plus clarithromycin	55% [48, 62] (n=187)	52% [45, 59] (n=215)
193	NEXIUM plus amoxicillin and clarithromycin	85%** [74, 93] (n=67)	78%** [67, 87] (n=74)
	NEXIUM	5% [0, 23] (n=22)	4% [0, 21] (n=24)

[†] Patients were included in the analysis if they had *H. pylori* infection documented at baseline, had at least one endoscopically verified duodenal ulcer ≥ 0.5 cm in diameter at baseline or had a documented history of duodenal ulcer disease within the past 5 years, and were not protocol violators. Patients who dropped out of the study due to an adverse event related to the study drug were included in the analysis as not *H. pylori* eradicated.
[‡] Patients were included in the analysis if they had documented *H. pylori* infection at baseline, had at least one documented duodenal ulcer at baseline, or had a documented history of duodenal ulcer disease, and took at least one dose of study medication. All dropouts were included as not *H. pylori* eradicated.
*$p < 0.05$ compared to NEXIUM plus clarithromycin
**$p < 0.05$ compared to NEXIUM alone

The percentage of patients with a healed baseline duodenal ulcer by 4 weeks after the 10 day treatment regimen in the NEXIUM plus amoxicillin and clarithromycin group was 75% (n=156) and 57% (n=60) respectively, in the 191 and 193 studies (per-protocol analysis).

INDICATIONS AND USAGE

Treatment of Gastroesophageal Reflux Disease (GERD)

Healing of Erosive Esophagitis

NEXIUM is indicated for the short-term treatment (4 to 8 weeks) in the healing and symptomatic resolution of diagnostically confirmed erosive esophagitis. For those patients who have not healed after 4-8 weeks of treatment, an additional 4-8-week course of NEXIUM may be considered.

Maintenance of Healing of Erosive Esophagitis

NEXIUM is indicated to maintain symptom resolution and healing of erosive esophagitis. Controlled studies do not extend beyond 6 months.

Symptomatic Gastroesophageal Reflux Disease

NEXIUM is indicated for treatment of heartburn and other symptoms associated with GERD.

H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence

Triple Therapy (NEXIUM plus amoxicillin and clarithromycin): NEXIUM, in combination with amoxicillin and clarithromycin, is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or history of within the past 5 years) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. (See **CLINICAL STUDIES** and **DOSAGE AND ADMINISTRATION**.)

In patients who fail therapy, susceptibility testing should be done. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted. (See **CLINICAL PHARMACOLOGY, Microbiology** and the clarithromycin package insert, **CLINICAL PHARMACOLOGY, Microbiology**.)

CONTRAINDICATIONS

NEXIUM is contraindicated in patients with known hypersensitivity to any component of the formulation or to substituted benzimidazoles.

Clarithromycin is contraindicated in patients with a known hypersensitivity to any macrolide antibiotic.

Concomitant administration of clarithromycin with pimozide is contraindicated. There have been post-marketing reports of drug interactions when clarithromycin and/or erythromycin are co-administered with pimozide resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsade de pointes) most likely due to inhibition of hepatic metabolism of pimozide by erythromycin and clarithromycin. Fatalities have been reported. (Please refer to full prescribing information for clarithromycin.)

Amoxicillin is contraindicated in patients with a known hypersensitivity to any penicillin. (Please refer to full prescribing information for amoxicillin.)

WARNINGS

CLARITHROMYCIN SHOULD NOT BE USED IN PREGNANT WOMEN EXCEPT IN CLINICAL CIRCUMSTANCES WHERE NO ALTERNATIVE THERAPY IS APPROPRIATE. IF PREGNANCY OCCURS WHILE TAKING CLARITHROMYCIN, THE PATIENT SHOULD BE APPRISED OF THE POTENTIAL HAZARD TO THE FETUS. (See WARNINGS in prescribing information for clarithromycin.)

Amoxicillin: Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more apt to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens.

There have been well documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before initiating therapy with any penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, amoxicillin should be discontinued and the appropriate therapy instituted.

SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin and amoxicillin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile colitis.*

PRECAUTIONS

General

Symptomatic response to therapy with NEXIUM does not preclude the presence of gastric malignancy.

Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with omeprazole, of which NEXIUM is an enantiomer.

Information for Patients

Patients should be informed of the following:
NEXIUM Delayed-Release Capsules should be taken at least one hour before meals.

For patients who have difficulty swallowing capsules, one tablespoon of applesauce can be added to an empty bowl and the NEXIUM Delayed-Release Capsule can be opened, and the pellets inside the capsule carefully emptied onto the applesauce. The pellets should be mixed with the applesauce and then swallowed immediately. The applesauce used should not be hot and should be soft enough to be swallowed without chewing. The pellets should not be chewed or crushed. The pellet/applesauce mixture should not be stored for future use.

Antacids may be used while taking NEXIUM.

Drug Interactions

Esomeprazole is extensively metabolized in the liver by CYP2C19 and CYP3A4.

In vitro and *in vivo* studies have shown that esomeprazole is not likely to inhibit CYPs 1A2, 2A6, 2C9, 2D6, 2E1 and 3A4. No clinically relevant interactions with drugs metabolized by these CYP enzymes

would be expected. Drug interaction studies have shown that esomeprazole does not have any clinically significant interactions with phenytoin, warfarin, quinidine, clarithromycin or amoxicillin.

Esomeprazole may potentially interfere with CYP2C19, the major esomeprazole metabolizing enzyme. Coadministration of esomeprazole 30 mg and diazepam, a CYP2C19 substrate, resulted in a 45% decrease in clearance of diazepam. Increased plasma levels of diazepam were observed 12 hours after dosing and onwards. However, at that time, the plasma levels of diazepam were below the therapeutic interval, and thus this interaction is unlikely to be of clinical relevance.

Esomeprazole inhibits gastric acid secretion. Therefore, esomeprazole may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (eg, ketoconazole, iron salts and digoxin).

Coadministration of oral contraceptives, diazepam, phenytoin, or quinidine did not seem to change the pharmacokinetic profile of esomeprazole.

Combination Therapy with Clarithromycin
Co-administration of esomeprazole, clarithromycin, and amoxicillin has resulted in increases in the plasma levels of esomeprazole and 14-hydroxyclarithromycin. (See **CLINICAL PHARMACOLOGY**, Pharmacokinetics: Combination Therapy with Antimicrobials.)

Concomitant administration of clarithromycin with pimozide is contraindicated. (See clarithromycin package insert.)

Carcinogenesis, Mutagenesis, Impairment of Fertility
The carcinogenic potential of esomeprazole was assessed using omeprazole studies. In two 24-month oral carcinogenicity studies in rats, omeprazole at daily doses of 1.7, 3.4, 13.8, 44.0 and 140.8 mg/kg/day (about 0.7 to 57 times the human dose of 20 mg/day expressed on a body surface area basis) produced gastric ECL cell carcinoids in a dose-related manner in both male and female rats; the incidence of this effect was markedly higher in female rats, which had higher blood levels of omeprazole. Gastric carcinoids seldom occur in the untreated rat. In addition, ECL cell hyperplasia was present in all treated groups of both sexes. In one of these studies, female rats were treated with 13.8 mg omeprazole/kg/day (about 5.6 times the human dose on a body surface area basis) for 1 year, then followed for an additional year without the drug. No carcinoids were seen in these rats. An increased incidence of treatment-related ECL cell hyperplasia was observed at the end of 1 year (94% treated vs 10% controls). By the second year the difference between treated and control rats was much smaller (46% vs 26%) but still showed more hyperplasia in the treated group. Gastric adenocarcinoma was seen in one rat (2%). No similar tumor was seen in male or female rats treated for 2 years. For this strain of rat no similar tumor has been noted historically, but a finding involving only one tumor is difficult to interpret. A 78-week mouse carcinogenicity study of omeprazole did not show increased tumor occurrence, but the study was not conclusive.

Esomeprazole was negative in the Ames mutation test, in the *in vivo* rat bone marrow cell chromosome aberration test, and the *in vivo* mouse micronucleus test. Esomeprazole, however, was positive in the *in vitro* human lymphocyte chromosome aberration test. Omeprazole was positive in the *in vitro* human

lymphocyte chromosome aberration test, the *in vivo* mouse bone marrow cell chromosome aberration test, and the *in vivo* mouse micronucleus test.

The potential effects of esomeprazole on fertility and reproductive performance were assessed using omeprazole studies. Omeprazole at oral doses up to 138 mg/kg/day in rats (about 56 times the human dose on a body surface area basis) was found to have no effect on reproductive performance of parental animals.

Pregnancy

Teratogenic Effects. Pregnancy Category B

Teratology studies have been performed in rats at oral doses up to 280 mg/kg/day (about 57 times the human dose on a body surface area basis) and in rabbits at oral doses up to 86 mg/kg/day (about 35 times the human dose on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to esomeprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Teratology studies conducted with omeprazole in rats at oral doses up to 138 mg/kg/day (about 56 times the human dose on a body surface area basis) and in rabbits at doses up to 69 mg/kg/day (about 56 times the human dose on a body surface area basis) did not disclose any evidence for a teratogenic potential of omeprazole. In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (about 5.5 to 56 times the human dose on a body surface area basis) produced dose-related increases in embryo-lethality, fetal resorptions, and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole at 13.8 to 138.0 mg/kg/day (about 5.6 to 56 times the human doses on a body surface area basis). There are no adequate and well-controlled studies in pregnant women. Sporadic reports have been received of congenital abnormalities occurring in infants born to women who have received omeprazole during pregnancy.

Amoxicillin

Pregnancy Category B. See full prescribing information for amoxicillin before using in pregnant women.

Clarithromycin

Pregnancy Category C. See **WARNINGS** (above) and full prescribing information for clarithromycin before using in pregnant women.

Nursing Mothers

The excretion of esomeprazole in milk has not been studied. However, omeprazole concentrations have been measured in breast milk of a woman following oral administration of 20 mg. Because esomeprazole is likely to be excreted in human milk, because of the potential for serious adverse reactions in nursing infants from esomeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the total number of patients who received NEXIUM in clinical trials, 778 were 65 to 74 years of age and 124 patients were ≥ 75 years of age.

No overall differences in safety and efficacy were observed between the elderly and younger individuals, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

The safety of NEXIUM was evaluated in over 10,000 patients (aged 18-84 years) in clinical trials worldwide including over 7,400 patients in the United States and over 2,600 patients in Europe and Canada. Over 2,900 patients were treated in long-term studies for up to 6-12 months. In general, NEXIUM was well tolerated in both short and long-term clinical trials.

The safety in the treatment of healing of erosive esophagitis was assessed in four randomized comparative clinical trials, which included 1,240 patients on NEXIUM 20 mg, 2,434 patients on NEXIUM 40 mg, and 3,008 patients on omeprazole 20 mg daily. The most frequently occurring adverse events (≥1%) in all three groups was headache (5.5, 5.0, and 3.8, respectively) and diarrhea (no difference among the three groups). Nausea, flatulence, abdominal pain, constipation, and dry mouth occurred at similar rates among patients taking NEXIUM or omeprazole.

Additional adverse events that were reported as possibly or probably related to NEXIUM with an incidence < 1% are listed below by body system:

Body as a Whole: abdomen enlarged, allergic reaction, asthenia, back pain, chest pain, chest pain substernal, facial edema, peripheral edema, hot flushes, fatigue, fever, flu-like disorder, generalized edema, leg edema, malaise, pain, rigors; ***Cardiovascular***: flushing, hypertension, tachycardia; ***Endocrine***: goiter; ***Gastrointestinal***: bowel irregularity, constipation aggravated, dyspepsia, dysphagia, dysplasia GI, epigastric pain, eructation, esophageal disorder, frequent stools, gastroenteritis, GI hemorrhage, GI symptoms not otherwise specified, hiccup, melena, mouth disorder, pharynx disorder, rectal disorder, serum gastrin increased, tongue disorder, tongue edema, ulcerative stomatitis, vomiting; ***Hearing:*** earache, tinnitus; ***Hematologic***: anemia, anemia hypochromic, cervical lymphoadenopathy, epistaxis, leukocytosis, leukopenia, thrombocytopenia; ***Hepatic***: bilirubinemia, hepatic function abnormal, SGOT increased, SGPT increased; ***Metabolic/Nutritional:*** glycosuria, hyperuricemia, hyponatremia, increased alkaline phosphatase, thirst, vitamin B12 deficiency, weight increase, weight decrease; ***Musculoskeletal***: arthralgia, arthritis aggravated, arthropathy, cramps, fibromyalgia syndrome, hernia, polymyalgia rheumatica; ***Nervous System/Psychiatric***: anorexia, apathy, appetite increased, confusion, depression aggravated, dizziness, hypertonia, nervousness, hypoesthesia, impotence, insomnia, migraine, migraine aggravated, paresthesia, sleep disorder, somnolence, tremor, vertigo, visual field defect; ***Reproductive***: dysmenorrhea, menstrual disorder, vaginitis; ***Respiratory***: asthma aggravated, coughing, dyspnea, larynx edema, pharyngitis, rhinitis, sinusitis; ***Skin and Appendages***: acne, angioedema, dermatitis, pruritus, pruritus ani, rash, rash erythematous, rash maculo-papular, skin inflammation, sweating increased, urticaria; ***Special Senses:*** otitis media, parosmia, taste loss, taste perversion; ***Urogenital***: abnormal urine, albuminuria, cystitis, dysuria, fungal

infection, hematuria, micturition frequency, moniliasis, genital moniliasis, polyuria; ***Visual***: conjunctivitis, vision abnormal.

Endoscopic findings that were reported as adverse events include: duodenitis, esophagitis, esophageal stricture, esophageal ulceration, esophageal varices, gastric ulcer, gastritis, hernia, benign polyps or nodules, Barrett's esophagus, and mucosal discoloration.

The incidence of treatment-related adverse events during 6-month maintenance treatment was similar to placebo. There were no differences in types of related adverse events seen during maintenance treatment up to 12 months compared to short-term treatment.

Two placebo-controlled studies were conducted in 710 patients for the treatment of symptomatic gastroesophageal reflux disease. The most common adverse events that were reported as possibly or probably related to NEXIUM were diarrhea (4.3%), headache (3.8%), and abdominal pain (3.8%).

Other adverse events not observed with NEXIUM, but occurring with omeprazole can be found in the omeprazole package insert, **ADVERSE REACTIONS** section.

Combination Treatment with Amoxicillin and Clarithromycin

In clinical trials using combination therapy with NEXIUM plus amoxicillin and clarithromycin, no adverse events peculiar to these drug combinations were observed. Adverse events that occurred have been limited to those that had been observed with either NEXIUM, amoxicillin, or clarithromycin alone.

The most frequently reported drug-related adverse events for patients who received triple therapy for 10 days were diarrhea (9.2%), taste perversion (6.6%), and abdominal pain (3.7%). No treatment-emergent adverse events were observed at higher rates with triple therapy than were observed with NEXIUM alone.

For more information on adverse events with amoxicillin or clarithromycin, refer to their package inserts, ADVERSE REACTIONS sections.

Laboratory Events

The following potentially clinically significant laboratory changes in clinical trials, irrespective of relationship to NEXIUM, were reported in ≤ 1% of patients: increased creatinine, uric acid, total bilirubin, alkaline phosphatase, ALT, AST, hemoglobin, white blood cell count, platelets, serum gastrin, potassium, sodium, thyroxine and thyroid stimulating hormone (see **CLINICAL PHARMACOLOGY**, *Endocrine effects* for further information on thyroid effects). Decreases were seen in hemoglobin, white blood cell count, platelets, potassium, sodium, and thyroxine.

In clinical trials using combination therapy with NEXIUM plus amoxicillin and clarithromycin, no additional increased laboratory abnormalities particular to these drug combinations were observed.

For more information on laboratory changes with amoxicillin or clarithromycin, refer to their package inserts, **ADVERSE REACTIONS** section.

OVERDOSAGE

A single oral doses of esomeprazole at 510 mg/kg (about 103 times the human dose on a body surface area basis), was lethal to rats. The major signs of acute toxicity were reduced motor activity, changes in respiratory frequency, tremor, ataxia, and intermittent clonic convulsions.

There have been no reports of overdose with esomeprazole. Reports have been received of overdosage with omeprazole in humans. Doses ranged up to 2,400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience (see omeprazole package insert - **ADVERSE REACTIONS**). No specific antidote for esomeprazole is known. Since esomeprazole is extensively protein bound, it is not expected to be removed by dialysis. In the event of overdosage, treatment should be symptomatic and supportive.

As with the management of any overdose, the possibility of multiple drug ingestion should be considered. For current information on treatment of any drug overdose, a certified Regional Poison Control Center should be contacted. Telephone numbers are listed in the Physicians' Desk Reference (PDR) or local telephone book.

DOSAGE AND ADMINISTRATION

The recommended adult dosages are outlined in the table below. NEXIUM Delayed-Release Capsules should be swallowed whole and taken at least one hour before eating.

For patients who have difficulty swallowing capsules, one tablespoon of applesauce can be added to an empty bowl and the NEXIUM Delayed-Release Capsule can be opened, and the pellets inside the capsule carefully emptied onto the applesauce. The pellets should be mixed with the applesauce and then swallowed immediately. The applesauce used should not be hot and should be soft enough to be swallowed without chewing. The pellets should not be chewed or crushed. The pellet/applesauce mixture should not be stored for future use.

The pellets have also been shown *in vitro* to remain intact when exposed to tap water, orange juice, apple juice and yogurt.

Recommended Adult Dosage Schedule of NEXIUM

Indication	Dose	Frequency
Gastroesophageal Reflux Disease (GERD)		
Healing of Erosive Esophagitis	20 mg or 40 mg	Once Daily for 4 to 8 Weeks*
Maintenance of Healing of Erosive Esophagitis	20mg	Once Daily**
Symptomatic Gastroesophageal Reflux Disease	20 mg	Once Daily for 4 Weeks***
***H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence**		
Triple Therapy:		
NEXIUM	40 mg	Once Daily for 10 Days
Amoxicillin	1000 mg	Twice Daily for 10 Days
Clarithromycin	500 mg	Twice Daily for 10 Days

*(see **CLINICAL STUDIES**). The majority of patients are healed within 4 to 8 weeks. For patients who do not heal after 4-8 weeks, an additional 4-8 weeks of treatment may be considered.
**Controlled studies did not extend beyond six months.
***If symptoms do not resolve completely after 4 weeks, an additional 4 weeks of treatment may be considered.

Please refer to amoxicillin and clarithromycin full prescribing information for **CONTRAINDICATIONS, WARNINGS** and dosing in elderly and renally-impaired patients.

Special Populations

Geriatric: No dosage adjustment is necessary. (See **CLINICAL PHARMACOLOGY, Pharmacokinetics.**)

Renal Insufficiency: No dosage adjustment is necessary. (See **CLINICAL PHARMACOLOGY, Pharmacokinetics.**)

Hepatic Insufficiency: No dosage adjustment is necessary in patients with mild to moderate liver impairment (Child Pugh Classes A and B). For patients with severe liver impairment (Child Pugh Class C), a dose of 20 mg of NEXIUM should not be exceeded (See **CLINICAL PHARMACOLOGY, Pharmacokinetics.**)

Gender: No dosage adjustment is necessary. (See **CLINICAL PHARMACOLOGY, Pharmacokinetics.**)

HOW SUPPLIED

NEXIUM Delayed-Release Capsules, 20 mg, are opaque, hard gelatin, amethyst colored capsules with two radial bars in yellow on the cap and 20 mg in yellow on the body. They are supplied as follows:

NDC 0186-5020-31 unit of use bottles of 30
NDC 0186-5022-28 unit dose packages of 100
NDC 0186-5020-54 bottles of 90
NDC 0186-5020-68 bottles of 100
NDC 0186-5020-82 bottles of 1000

NEXIUM Delayed-Release Capsules, 40 mg, are opaque, hard gelatin, amethyst colored capsules with three radial bars in yellow on the cap and 40 mg in yellow on the body. They are supplied as follows:

NDC 0186-5040-31 unit of use bottles of 30
NDC 0186-5042-28 unit dose packages of 100
NDC 0186-5040-68 bottles of 100
NDC 0186-5040-82 bottles of 1000

Storage

Store at 25°C (77°F); excursions permitted to 15 - 30°C (59 - 86°F). [See USP Controlled Room Temperature]. Keep container tightly closed. Dispense in a tight container if the product package is subdivided.

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically. Fifth Edition: Approved Standard NCCLS Document M7-A5, Vol. 20, no. 2, NCCLS, Wayne, PA, January 2000.

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AstraZeneca LP
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Rev. 02/01

AstraZeneca